

REMARKS

Applicant respectfully requests reconsideration.

Claims 1-17, 64, 65 and 67 were pending in this application. Claims 6, 7 and 67 have been withdrawn as being drawn to nonelected inventions. Claims 1, 15, 64 and 65 have been amended. Claims 72-75 are newly added claims. Support for the amendments and the new claims can be found in the specification, for example, on page 13, lines 21-27; page 16, lines 17-18; page 18, lines 16-24; page 19, lines 23-25; page 23, lines 19-20; page 28, lines 2-4, and line 27; page 60, lines 5-7 and in the claims as originally filed. Applicant reserves the right to pursue the subject matter of the originally filed claims in one or more continuing applications. Claims 1-5, 8-17, 64-65 and 72-75 are currently under examination.

The specification has been amended to add sequence identifiers and to remove hyperlinks.

No new matter has been added.

Interview Summary

On July 14, 2008, Nicole Hawes, assistant to the undersigned, contacted the Examiner by phone and requested a Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequences and/or Amino Acid Sequence Disclosures referred to in the instant Office Action. The Examiner stated that no Notice was mailed because the reasons for the objection to the sequence disclosures were laid out in the Office Action. Applicant respectfully thanks the Examiner for this clarification.

Objections to the Specification

The Examiner has objected to the disclosure because it contains embedded hyperlinks. Applicant has amended the specification to remove these hyperlinks.

The Examiner has further objected to the disclosure because it contains sequences that are not identified by a sequence identifier. Applicant has amended the specification to add the missing sequence identifiers and provides a substitute Sequence Listing herewith. Applicant requests entry of the substitute Sequence Listing. The substitute Sequence Listing contains no new matter.

Accordingly, reconsideration and withdrawal of the objections to the specification is respectfully requested.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1-5, 8-17 and 64-65 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicant respectfully traverses. Applicant submits that the previously pending claims met the written description requirement. The previously pending claims were drawn to methods of treating a subject having an HCV infection that was not successfully treated using a previous non-CpG therapy by administering a CpG immunostimulatory nucleic acid. The specification teaches the genus of CpG oligonucleotides and species within that genus, it defines subject populations to be treated and the non-CpG therapies such subjects would have received, and it teaches administration and treatment regimes. In view thereof, Applicant had possession of the subject matter of the rejected claims, as previously pending, at the time of filing.

Nevertheless, without conceding the correctness of the Examiner's argument and solely in the interest of expediting prosecution, Applicant has amended independent claims 1, 15, 64 and 65 to recite methods of stimulating an immune response in a human subject having an HCV infection that was not successfully treated with a previous non-CpG therapy by administering CpG immunostimulatory nucleic acids (claims 1 and 15) and methods of controlling viral replication and viral spread in a human subject having an HCV infection that was not successfully treated with a previous non-CpG therapy by administering CpG immunostimulatory nucleic acids and an antiviral agent (claims 64 and 65). Applicant has further amended the claims to recite structural features of the CpG immunostimulatory nucleic acid. Support for these amendments can be found, for example, on page 13, lines 21-27; page 16, lines 17-18; page 18, lines 16-24; page 19, lines 23-25; page 23, lines 19-20; page 28, lines 2-4, and line 27; page 60, lines 5-7 of the specification.

The relevant inquiry in analyzing written description is whether the specification "clearly allows persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed" (*In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)) or, in other words, that the

applicant was in “possession” of the invention (*In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996)).

With respect to the claims as now amended, the specification describes the nature of the stimulated immune response and how it may be measured, for example on pages 16-17 and 19-20. Although not required for written description, the specification further provides *in vitro* working examples (see pages 57-59) of immune response induction by CpG oligonucleotides, using isolated peripheral blood mononuclear cells (PBMCs) derived from chronic HCV carriers. The specification extensively describes the structure, and provides many examples, of CpG oligonucleotides (see for example pages 22-44, as well as Table 2, page 55 for oligonucleotides used in the working examples). The specification correlates the structure of the CpG oligonucleotides with their function in stimulating an immune response in chronic HCV carriers. The specification therefore demonstrates that Applicant was in the possession of “the primary active ingredient” for the claimed invention, that is CpG oligonucleotides that stimulate an immune response in chronic HCV carriers, at the time of filing.

The specification further correlates viral clearance with the type and strength of immune responses induced in PBMCs from chronic HCV carriers following contact with CpG oligonucleotides. The specification discloses examples of antiviral agents, e.g. on pages 18-19 and page 47. The specification also describes the use of CpG oligonucleotides in combination with such antiviral agents and provides data from *in vitro* experiments showing immune response induction, see e.g. pages 59-62.

Therefore, based on the teachings and working examples provided in the specification, one of ordinary skill in the art would recognize that Applicant had, at the time of filing, possession of methods of stimulating an immune response in a human subject having an HCV infection that was not successfully treated using a previous non-CpG therapy comprising administering CpG immunostimulatory nucleic acids, and methods of controlling viral replication and viral spread in a human subject having an HCV infection that was not successfully treated using a previous non-CpG therapy comprising administering CpG immunostimulatory nucleic acids and an antiviral agent.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner has rejected claims 1-5, 8-17 and 64-65 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner contends that “the specification at the time the application was filed would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation”.

Applicant respectfully traverses. Applicant submits that the previously pending claims were fully enabled. Nevertheless, without conceding the correctness of the Examiner’s argument and solely in the interest of expediting prosecution, Applicant has amended independent claims 1, 15, 64 and 65 to recite methods of stimulating an immune response in a human subject having an HCV infection that was not successfully treated with a previous non-CpG therapy by administering CpG immunostimulatory nucleic acids (claims 1 and 15) and methods of controlling viral replication and viral spread in a human subject having an HCV infection that was not successfully treated with a previous non-CpG therapy by administering CpG immunostimulatory nucleic acids and an antiviral agent (claims 64 and 65). Support for these amendments can be found, for example, on page 13, lines 21-27; page 16, lines 17-18; page 18, lines 16-24; page 19, lines 23-25; page 23, lines 19-20; page 28, lines 2-4, and line 27; page 60, lines 5-7 of the specification.

Claims are enabled if one of ordinary skill in the pertinent art can practice (i.e., make and use) the subject matter of the claims without undue experimentation. Factors to be considered in determining whether experimentation is undue include the nature of the invention, the breadth of the claims, the amount of direction or guidance presented, the relative skill in the art, the state of the art, the predictability in the art, the presence of working examples, and the quantity of experimentation necessary. (*In re Wands*, 858 F.2d 731 USPQ2nd 1400 (Fed. Cir, 1988)). The factors are to be considered in their totality with no one factor being dispositive.

Applicant submits that, in view of the state of and level of predictability in the art, the specification provides sufficient guidance and working examples to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation.

Nature of the invention. The claimed invention is directed to the use of oligonucleotides comprising a CpG motif to stimulate immune cells from subjects having an HCV infection that were not successfully treated with a previous non-CpG therapy.

Breath of the claims. The amended claims are drawn to methods of stimulating an immune response and methods of controlling viral replication and viral spread in human subjects having an HCV infection that were not successfully treated with a previous non-CpG therapy. These methods involve administering immunostimulatory CpG oligonucleotides in the presence or absence of an antiviral agent. Applicant submits that the scope of the claims is fully commensurate with the disclosure of the specification.

Amount of direction or guidance presented. With respect to the claims as now amended, the specification describes subject populations, non-CpG therapies (pages 11-14), the nature of the stimulated immune response and how it may be measured (pages 16-17 and 19-20), examples of CpG oligonucleotides (pages 22-44 and Table 2, page 55), examples of antiviral agents (pages 18-19, and page 47), administration routes, dosages, and formulations (pages 49-54 and 59-62). Applicant submits that the specification contains sufficient direction and guidance for one of ordinary skill in the art to practice the claimed methods.

Level of skill in the art. The level of ordinary skill of those in the art is generally that of an M.D. and/or a Ph.D.

State of the art and predictability in the art. With regard to the alleged unpredictability of immune response induction by CpG oligonucleotides, Applicant points out that the specification provides *in vitro* data demonstrating immune profiles induced from chronic HCV PBMC using many CpG oligonucleotides. These data evidence immune response induction by CpG oligonucleotides in PBMCs from human chronic HCV carriers. As discussed in greater detail herein, one of the CpG oligonucleotides provided by the specification was actually used in clinical trials involving chronic HCV carriers. These data therefore refute the Examiner's assertion of unpredictability.

Applicant submits that the state of the art supports immune response induction in chronic HCV carriers, as now recited in the claims. Each of the Examiner's points, as well as the cited references, are discussed below.

With regard to the Examiner's arguments about the many challenges in the field of HCV infection, for example the alleged lack of an effective cell culture system or the absence of an animal model besides humans and chimpanzees, Applicant respectfully points out that the specification teaches *in vitro* cell culture assays using PBMCs isolated from human chronic HCV

carriers to measure immune responses upon contact with CpG oligonucleotides. The specification teaches that all classes of CpG oligonucleotides (A, B, C class) induce Th1-type responses and provides evidence of the immune stimulation of PBMCs from HCV-infected human carriers. The Examiner concedes that “the involvement of a Th1-type immune response in combating against intracellular pathogens is a *well-recognized general concept*” and that the “art acknowledges the importance of Th1-type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, *including viruses*” (see page 8 of the Office Action, emphasis added).

The Examiner cites Infante-Duarte et al. (Springer Seminars in Immunopathology, 1999, 21:317-338) for the teaching that “in addition to a Th1 type immune response, a Th2 type immune response is also necessary.” Applicant submits that Infante-Duarte et al. describes Th1 and Th2-type responses for various pathogens, but does not teach the relative importance of Th1 versus Th2 responses in chronic HCV infections. Infante-Duarte et al. teaches that viral infections strongly induce type I IFNs, such as IFN- α and IFN- β (see page 325, 2nd paragraph). The instant specification teaches that CpG oligonucleotides exert their antiviral effects at least in part through induction of cytokines such as IFN- α and IFN- γ and of Th1-type HCV-specific immune responses (see, page 60, lines 5-7). Therefore, the teachings of Infante-Duarte et al. on viral infections are consistent with the teachings provided in the instant specification and they support rather than refute enablement.

The Examiner cites Aoki et al. (Expert Opin. Emerg. Drugs, 2004, Vol. 9, No. 2, 223-236), Bohn et al. (Infect. Immun., 1998, Vol. 66, 2213-2220), Sakao et al. (Int. Immunol., 1999, Vol. 11, 471-480), Zaitseva et al. (Blood, 2000, Vol. 96, 3109-3117), and Masihi (Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653) for the proposition that single cytokine therapy against intracellular pathogens may not be effective. Respectfully, the claimed methods are drawn to administering immunostimulatory CpG oligonucleotides and not specific single cytokines. The relevance of these references is therefore unclear particularly in view of the art-recognized fact that CpG oligonucleotides induce a broad immune response profile, including induction of a number of cytokines (rather than any single cytokine) and stimulation of various cell types. The instant specification also teaches that “the controlled release of different type I IFN isoforms by specific CpG ODN [oligonucleotides] in vivo is superior to the systemic administration of

recombinant type I IFN that is of a single subtype" (see page 60, lines 14-16). The immune response induced by CpG oligonucleotides is a balanced response, as contrasted with the immune response induced by single cytokines.

Aoki et al. states that "type I IFNs (IFN- α/β) have been widely used for treating hepatitis B and C infections" (see, page 226, left column, 3rd paragraph) and lists in Table 1 (on page 230) a number of IFN- α , β , and γ agonists in various stages of clinical trials (Phase I, II, and III) for the treatment of Hepatitis C. The teachings in Aoki et al. concerning HCV infections are consistent with the teachings provided in the instant specification.

Masihi states that "*efficacy and safety* of a combination therapy of IFN- α and ribavirin for treatment of chronic hepatitis C virus (HCV) in HIV-seropositive patients has been recently reported. Combination therapy with IFN and ribavirin was effective in 50% of cases clearing HCV RNA" (see page 645, paragraph spanning left and right column, emphasis added). Masihi does not teach that administration of one or more particular cytokines in chronic HCV carriers is "inherently toxic", has "unclear pharmacological behavior" or has "pleiotropic effects" as suggested by the Examiner (apparently with reference to page 646, left column, last paragraph). Masihi further states that "it is possible to use CpG DNA as an immunomodulator for therapeutic applications since it induces a predominantly Th1 pattern of immune activation" (see, page 646, right column, 2nd paragraph).

The instant specification teaches that an antiviral-like, Th1-type immune response similar to the Th1-type response in healthy individuals can be stimulated in immune cells isolated from chronically HCV infected human subjects that did not respond to previously administered non-CpG treatment (such as e.g. IFN- α and ribavirin). The instant specification teaches further that "when CpG ODN [oligonucleotide] was used in combination with Intron-A [IFN- α -2b], a synergistic effect was observed for IFN- α secretion from PBMCs from HCV infected subjects" (see paragraph spanning pages 60 and 61). Therefore, the teachings in Masihi concerning HCV infections are consistent with the teachings provided in the instant specification.

The teachings of Bohn et al., Sakao et al., and Zaitseva et al. are not relevant to the subject matter of the rejected claims because these teachings relate to the role of certain

cytokines (IL-12, IL-18, IFN- γ and IL-6, respectively) in bacterial or HIV infections and do not contain teachings relating to the use of CpG oligonucleotides.

The Examiner cites Krieg et al. (Annu. Rev. Immunol., 2002, Vol. 20, 709-760) and Mutwiri et al. (Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103) to support the position that the level and type of immune stimulation varies between CpG oligonucleotides, that CpG sequences are species-specific, and that cellular recognition varies between species. Without conceding the Examiner's position and characterization of the references, Applicant submits that independent claims 1, 15, 64 and 65 have been amended to recite "human" subjects. The specification provides *in vitro* data comparing immune profiles in primary cells from human chronic HCV carriers of at least 16 different CpG oligonucleotides of three different classes of CpG oligonucleotides (A, B, and C class), comprising different sequences and/or different backbone linkages (e.g., those listed in Table 2, page 55). The teachings of Krieg et al. and Mutwiri et al. are consistent with the scope of the rejected claims, and therefore they support rather than refute enablement of these claims.

The Examiner argues that "efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive," citing Yamamoto et al. (Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40), Equils et al. (J. Immunol. 2003, 170, 5159-5164), Agrawal et al. (J. Immunol. 2003, 171, 1621-1621), and Olbrich et al. (J. Virol., 2003, 77, 10658-10662).

Yamamoto et al. report that many CpG containing oligonucleotides (of different length and nucleotide sequence) induce an immune response in mice and humans. The remaining teachings in Yamamoto et al. relating to influenza virus are not relevant to the instant claims which recite HCV. The teachings of Equils et al. and Agrawal et al. relate to induction of HIV replication in HIV infected mice or humans, respectively, when treated with CpG-containing oligonucleotides. The teachings of Olbrich et al. relate to retroviral infection of mice with Friend retrovirus. Yamamoto et al., Equils et al., Agrawal et al., and Olbrich et al. (to the extent of its teachings relating to retroviral infections) do not provide teachings relevant to immune response induction in chronic HCV carriers. Even the teachings of Olbrich et al. relating to administration of CpG oligonucleotides prior to infection with virus are not relevant to the claimed invention

which recites subjects that have already been infected with virus (i.e., they are chronic virus carriers).

Applicant respectfully submits that the cited references do not evidence that immune stimulation by CpG oligonucleotides in chronic HCV carriers is unpredictable. To the contrary, the reference teachings are consistent with the teachings of the instant specification and support, rather than refute, enablement of the rejected claims.

Presence of working examples. The specification provides working examples demonstrating stimulation of an immune response in PBMCs derived from chronic HCV carriers using CpG oligonucleotides. The specification teaches that the immune response induced in the PBMCs is a Th1-type response. Th1-type immune responses are consistent with antiviral immune activity in healthy subjects (see, e.g. Infante-Duarte et al., and Aoki et al., cited by the Examiner). The Examiner acknowledges on page 7 of the Office Action that the specification contains “a working example evidencing the ability of the [CpG] oligonucleotide to induce Th1 immune response, including the production of IFN-alpha and gamma.” The specification also provides data showing the potentiating immunostimulatory effect of co-administration of CpG oligonucleotides and antiviral agents, such as IFN (see, e.g. page 11, lines 11-16, and page 59, lines 18-19). The specification provides *in vitro* data comparing immune profiles in primary human cells of at least 16 different CpG oligonucleotides of three different classes of CpG oligonucleotides (A, B, and C class), comprising different sequences and/or different backbone linkages (e.g. those listed in Table 2). The *in vitro* immunoassays of these working examples are an established *in vitro* model, the results of which generally correlate with *in vivo* immune response profiles. Thus, the working examples provided by the specification correlate with the scope of the rejected claims.

In addition to the working examples described in the specification, Applicant points out that Phase Ib and Phase II clinical trials, now discontinued, were conducted post-filing and showed that a CpG oligonucleotide (CpG 10101, Actilon™) disclosed in the instant specification as SEQ ID NO: 4 was generally well tolerated and led to a reduction in viral load and viral spreading, measured by the amount of plasma HCV RNA detected in chronic HCV carriers. The Phase II trial further established that the combination of CpG 10101 with IFN and ribavirin led to undetectable levels of HCV at 24 weeks in chronic HCV carriers that did not

previously respond to conventional, non-CpG therapy (see references cited in the IDS/1449, filed herewith). This post-filing data, generated by following the teachings of the specification, can be used to establish enablement of the claims at the time of filing. In re Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995); In re Wands, 858 F.2d 731.

These clinical trials were conducted in accordance with the teachings of the specification. The specification teaches that CpG oligonucleotides stimulate immune responses and provides data showing increased production of IFN- α , IFN- γ , and IP10 (see Example section and Figures 1-7). The Phase Ib trial showed dose-dependent cytokine induction, e.g. increases of IFN- α and IP10, after administration of CpG 10101. The specification teaches that a non-responder is a subject who has undergone previous non-CpG antiviral therapy, for example treatment with pegylated or non-pegylated alpha-interferons and ribavirin, and who still shows detectable HCV viral load in the bloodstream (see, pages 11 and 12). In the Phase II trial, the enrolled subjects had undergone combination treatments of pegylated alpha-interferons and ribavirin for 48 weeks and relapsed with detectable levels of viral RNA. The specification teaches typical dosage ranges from 0.5 to 500 μ g/kg for CpG oligonucleotides (see page 47, line 3). The Phase II trial was conducted using 200 μ g/kg CpG 10101. The specification teaches CpG oligonucleotides can be administered weekly for 3-12 months alone or in combination with pegylated or non-pegylated alpha-interferons (page 61, lines 29 – page 62, line 12). In the Phase II trial, CpG alone or in combination with IFN or IFN and ribavirin was given weekly for 12 weeks (3 month) and, in the case of viral titer reduction, for an additional 48 weeks (11 months).

It is apparent from these results that CpG oligonucleotides stimulate immune responses, and reduce the viral load in combination treatment with antiviral agents, in human chronic HCV carriers. A person of ordinary skill in the art following the teachings of the instant specification would be able to practice the claimed methods without undue experimentation, as evidenced at least in part by the post-filing data.

Quantity of experimentation necessary. Applicant respectfully submits that, in view of the teaching in the specification of subjects, CpG oligonucleotides, and induced immune responses, the quantity of experimentation required to practice the claimed methods is well within the range of experimentation that those in the art routinely engage in, and this is not undue.

The specification including the working examples provided therein present sufficient information and guidance to enable a person of ordinary skill in the art to practice the claimed invention in view of the predictability in the art relating to the claimed invention. The claims are therefore enabled.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and discussion, Applicants believe the pending application is now in condition for allowance. Allowance is respectfully requested.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825 (C1037.70035US01).

Respectfully submitted,



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